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TESTIMONY

Before

THE COMMISSIONER OF FOOD AND DRUGS
FDA AND STAKEHOLDERS PUBLIC MEETING

on

THE PRESCRIPTION DRUG USER FEE ACT

Presented by:

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I am Dr. Allan Korn, Senior Vice President, Clinical Affairs and Chief Medical Officer, of the Blue Cross and Blue Shield Association. The Blue Cross and Blue Shield Association represents the 46 independent Blue Cross and Blue Shield Plans that provide health coverage to over 75 million people - approximately one in four Americans. Blue Cross and Blue Shield Plans have extensive experience in providing prescription drug coverage through a variety of products. Thank you for the opportunity to appear before the Food and Drug Administration at today's public meeting on the Prescription Drug User Fee Act (PDUFA).

Although the *Federal Register* notice announcing today's meeting lists several areas that the FDA will examine as it considers what features it should advocate in proposing new or amended authorizing legislation, I will focus my remarks on the consumer safety aspects of PDUFA, and the statute's role in ensuring that the rapid flow of new drugs to market is accompanied by information that allows consumers, physicians and health plans to make value-driven prescription drug decisions.

Specifically, I will address the following question posed in the *Federal Register* notice for today's meeting:

- Should fees collected from industry be used to pay for other costs FDA incurs to ensure that drugs in the American marketplace are safe and effective? Such additional

costs might include monitoring adverse drug reactions, monitoring drug advertising, and routine surveillance, inspection and testing of drug manufacturers.

My testimony today focuses on:

(1) Background on PDUFA; and

(2) BCBSA's recommendations to expand PDUFA's definition of user fee-funded activities to include postmarketing surveillance and the monitoring of the risk and benefit information in direct-to-consumer (DTC) advertising as a user fee-funded activity.

I also propose that the FDA review PDUFA's role in ensuring that the rapid flow of new drugs to market is accompanied by information that allows consumers, physicians and health plans make value-driven prescription drug purchasing decisions. While this issue is slightly beyond the scope of this meeting, BCBSA believes that, given the need to ensure access to true breakthrough drugs, it is critical that consumers, clinicians, and government and private payers have the information they need to evaluate the benefits, costs and risks of new drug therapies compared to the benefits, costs and risks of drugs that replace therapies already on the market.

As the FDA re-examines its approach to DTC advertising compliance in the context of PDUFA, BCBSA recommends that the FDA support initiatives to require manufacturers to provide cost information along with benefit and risk information to consumers.

Background on PDUFA

In 1992, Congress passed the Prescription Drug User Fee Act, which authorized the FDA to collect user fees from prescription drug manufacturers seeking marketing approval for new products. Under PDUFA, the FDA collected $327 million in user fees during the five-year implementation period. It used these funds to hire 600 additional reviewers and upgrade the management systems in the premarket review program for branded prescription drugs in the Center for Drug Evaluation and Research (CDER) and biologics products in the Center for Biologics Evaluation and Research (CBER).

In exchange for this new funding, PDUFA required the FDA to meet rising annual performance targets. These targets were designed to ensure that the agency would upgrade its efficiency significantly between 1993 and September 1997, when a sunset provision terminated the program. The FDA faced the prospect of losing this important source of new funding unless it performed well enough to motivate Congress to reauthorize user fees in 1997. However, in 1997 Congress renewed user fee funding for five more years as part of the FDA Modernization Act (FDAMA). It is set to expire in September 2002.

Since the enactment of PDUFA, total approval time — the time from the initial submission of a marketing application to the issuance of an approval letter — has dropped from a median of 23 months to 12 months. Total approval time for priority

applications (applications for those products providing significant therapeutic gains) has dropped from a median of over 12 months in the early PDUFA years to six months.

In addition, because FDA has put greater effort into communicating what it expects applicants to submit, a higher percentage of applications are being approved. Before PDUFA, only about 60 percent of the applications submitted were ultimately approved. Now, about 80 percent are approved.

As a result, more new drugs are coming to the market faster than ever before. However, resources for important activities that ensure these new products are safe and effective for consumers have not kept pace with resources for drug review. PDUFA provides funding only for tasks that lead up to a decision on whether to approve or deny an NDA. Postmarketing regulatory activities stemming from fast-to-market approval of new drugs — such as tracking and responding to reports of adverse drug reactions and monitoring drug advertisements for compliance with agency regulations — are not covered by user fees. Thus, these critical consumer safety responsibilities must be paid for out of Congressional appropriations.

However, PDUFA currently requires that FDA spend as much appropriated money on drug review each year as it did in 1997, adjusted for inflation. If the FDA fails to meet this requirement, its legal authority to collect and spend user fees that year becomes void. As a practical matter, the FDA must spend slightly more from appropriations each year

on drug review than it spent in 1997 so that the statutory threshold is met when its accounting is complete.

Because FDA has not received increased congressional appropriations beyond the rate of inflation since 1994, spending of such funds on drug review to keep up with PDUFA adversely effects the FDA's core programs. This meeting is prompted in part by the FDA's stated concern that an unintended consequence of PDUFA's success in funding faster drug reviews is the erosion of consumer safety protections that the FDA can no longer fund from appropriated money.

Given the critical consumer safety functions the FDA performs, increased congressional appropriations are necessary and BCBSA believes that such additional funding would serve the public well.

BCBSA Recommendations

BCBSA recommends that Congress amend PDUFA to include postmarketing surveillance and compliance activities (e.g., monitoring adverse drug events and DTC advertising) under section 379(g)(6) in the statutory definition of "process[es] for the review of human drug applications." By expanding the definition of user fee-funded activities to include these critical regulatory responsibilities, Congress will ensure that consumers receive safe and effective prescription drugs and have complete and accurate information about the risks and benefits associated with their use.

Postmarketing Surveillance

BCBSA recommends that Congress amend PDUFA so that user fees will fund postmarketing surveillance activities associated with ongoing approval, including Phase IV safety studies. In addition, we believe Congress should require the FDA to develop a protocol to monitor adverse reactions related to drugs that carry a relatively higher risk.

PDUFA's emphasis on faster approval times was bolstered by FDAMA. FDAMA granted the FDA "fast track" authority, which permits faster approval times for certain drugs by allowing manufacturers to substitute surrogate markers of efficacy for actual clinical data. Working in tandem, PDUFA and FDAMA have decreased the combination of average review time and average clinical study time for new drugs approved in the late 1990s by more than two years compared to new drugs approved in the early 1990s, according to a recent study by the Tufts Center for the Study of Drug Development (CSDD).

Although the introduction of new drug therapies is exciting for physicians and patients, not all of a drug's potential side effects and interactions are known at the time of market entry. Instead, these manifest themselves gradually as the drug is accepted into clinical practice and used in a large patient population for the first time. A study of adverse drug reactions in hospitalized patients published by *JAMA* in April 1998 estimated that in 1994, 2.2 million hospitalized patients had adverse drug reactions and that 106,000 had fatal reactions.[i] The investigators concluded that such a level of mortality made adverse drug reactions at least the sixth leading cause of death in the United States.

Moreover, in 1998 the FDA removed several drugs from the market that had been approved under the "fast track" authority: the antihistamine Seldane; two obesity drugs, Pondimin and Redux (better known as "fen-phen"); and Duract, a prescription medication for pain.[ii] In March 2000, Warner Lambert withdrew Rezulin, a medication for diabetes that had also been approved under the fast track authority.[iii] These withdrawals have raised concern that the fast-track system does not have sufficient safeguards to protect the public from medicines with potentially dangerous interactions and side effects.[iv]

As new products flood the market under PDUFA, the volume of adverse event reports (AERs) is growing substantially. According to *CDER 1999 Report to the Nation*, the FDA received over 258,000 AERs in calendar year 1999. This level is more than twice the 118,000 AERs that the FDA received in 1992, and almost four times as many as the 68,000 received in 1989.[v]

BCBSA believes that an integral part of delivering new drug therapies to physicians and consumers is the postmarket monitoring of adverse events associated with consumer use of these drugs. As the FDA conceded in announcing this meeting, the agency lacks sufficient resources to adequately monitor reports of adverse events and conduct timely safety interventions (e.g., by issuing "Dear Doctor" letters or pulling the product from the market). By expanding the definition of user fee-funded activities to include this critical regulatory responsibility associated with review and approval, Congress will ensure consumers receive safe and effective prescription drugs.

DTC Advertising

BCBSA believes that consumers faced with a barrage of advertisements for new drugs entering the market as a result of user-fee funded reviews must receive clear and understandable information about their benefits and risks. As such, BCBSA recommends that Congress amend PDUFA to include monitoring of DTC advertising compliance under section 379(g)(6) in the statutory definition of "process[es] for the review of human drug applications." BCBSA further recommends that Congress require the FDA to develop criteria for the level and type of information that consumers need for advertised drugs.

As more new drugs reach the market faster under PDUFA, they are marketed directly to consumers. In 1999, pharmaceutical manufacturers spent $1.8 billion on DTC advertising. According to a 1999 study by National Institute for Healthcare Management (NIHCM), the 10 most heavily promoted drugs in 1998 accounted for over a fifth of the total growth in prescription drug expenditures from 1993 to 1998. In total, these 10 drugs had 1998 sales of over $11 billion – about 12 percent of all retail drug spending. This use-inducing advertising raises issues with respect to consumer safety in the absence of complete information about product benefits and risks.

Recent surveys raise questions about the effectiveness of DTC advertising in communicating pertinent information about drugs. The 1999 *Prevention* survey asked respondents who recalled seeing DTC ads to rate them on a four-point scale (with "don't

know" as a possible fifth response) on how well they communicate information about risks and benefits. Just one in eight consumers thought that DTC ads do an excellent job in conveying "serious warnings about the product." More than two-fifths of consumers rated magazine ads as doing "only fair" (30%) or "poor" (14%) jobs in communicating serious risks.

Half of the respondents thought that television ads do an "only fair" (30%) or "poor" (20%) job in communicating serious warnings. Similarly, one in eight consumers thought that magazine and television ads do an excellent job in communicating "annoying but not serious side effects." About half thought that DTC ads do an "only fair" or "poor" job at communicating such side effects.

Most physicians are also skeptical of the quality and objectivity of the information presented in the ads. In a 1998 survey of 3,000 doctors, Scott-Levin found that more than half of physicians disagreed with the statement, "DTC advertising is a reliable source of information." In addition, more than 60% disagreed with the statement, "DTC advertising is an objective source of information."[vi]

By expanding the definition of user fee-funded activities to include this critical regulatory responsibility, Congress will help ensure that consumers have more complete and accurate information about the risks and benefits associated with prescription drugs. This action should be supported by FDA development of criteria for the level and type of information that consumers need for advertised drugs.

Value Information

BCBSA recommends that the FDA review PDUFA's role in ensuring that the rapid flow of new drugs to market is accompanied by information that allows consumers, physicians and health plans make value-driven prescription drug decisions. Specifically, BCBSA recommends that the FDA support initiatives to require manufacturers to provide information that allows them to evaluate the benefits, costs and risks of new drug therapies that replace existing therapies compared to the benefits, costs and risks of the drugs already on the market.

Some of the drugs that reach the market faster under PDUFA will truly be breakthrough products – offering treatment where no effective treatment currently exists. These drugs are likely to be the treatment of choice by physicians and their patients, and will bring valuable benefits to individuals and their families. But other newly introduced drugs will substitute for existing drug treatments.

Because the marketplace is becoming more and more competitive within many therapeutic classes, relative cost-effectiveness information is becoming more important. Given the need to ensure access to the true breakthrough drugs, it is critical that consumers, clinicians, and government and private payers have the information they need to make value-driven prescription drug decisions.

Conclusion

BCBSA is very concerned that accelerated drug reviews under PDUFA have not been accompanied by comparable funding for consumer safety initiatives. BCBSA believes that as user fees speed new therapies to consumers, there is a comparable need to ensure that these drugs are safe and effective drugs and consumers receive complete and accurate information about the risks and benefits associated with their use.

In order to achieve this objective, BCBSA recommends that Congress amend the statutory definition of "process[es] for the review of human drug applications" to include as "activities necessary for the review of human drug applications and supplements" postmarketing surveillance and compliance activities (e.g., monitoring adverse drug events and DTC advertising) (21 USC §379(g)(6)(A)).

In addition, BCBSA recommends that the FDA review PDUFA's role in ensuring that the rapid flow of new drugs to market is accompanied by information that allows consumers, physicians and health plans make value-driven prescription drug decisions.

BCBSA applauds the FDA for addressing this critical health care issue and supports the agency in its endeavor.

[i] Jason Lazarou, MSc; Bruce H. Pomeranz, MD, PhD; Paul N. Corey, PhD, "Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies," *Journal of the American Medical Association* Vol. 279, No. 15 (April 15, 1998): 1200-1217.

[ii]Policy.com, "The FDA's 'Fast Track' Review Program," Pharmaceuticals (August 17, 1998): accessed June 16, 2000 from http://www.policy.com/issuewk/98/0817/081798e.html.

[iii] David Willman and Nick Anderson, "Rezulin's Swift Approval, Slow Removal Raise Issues," *Los Angeles Times* (March 23, 2000): accessed June 16, 2000 from http://www.latimes.com.

[iv] Linda F. Golodner, President, National Consumers League, "FDA Reform: A Consumer Perspective," Remarks provided at the 43rd Annual Ohio Pharmaceutical Seminar sponsored by the Ohio State University Health Services Center, College of Pharmacy, April 20, 1998. Accessed June 16, 2000 from http://www.natlconsumersleague.org/ohio.htm.

[v] Food and Drug Administration, Center for Drug Research and Evaluation, *CDER 1999 Report to the Nation: Improving Public Health Through Human Drugs*: 23. Accessed May 21, 2000 from http://www.fda.gov.

[vi] "Half of Rx drug consumer ad spending goes to TV, Scott-Levin reports." Cf. also "IMS Health Reports Direct-to-Consumer Advertising Increases Prescription Pharmaceutical Brand Requests and Awareness: Majority of Physicians have Negative View Toward DTC Advertising."